NNPDF Peter G. Pentchev Research Fellowship

Understanding the cellular mechanism of HDAC inhibitors for the treatment of NPC disease

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Niemann Pick type C disease is caused due to mutations in NPC1 or NPC2 protein resulting in an accumulation of cholesterol in the cells. We previously demonstrated that histone deacetylase inhibitors (SAHA and LBH589) can reduce cholesterol levels in NPC1 patient fibroblast (skin) cells and increase NPC1 protein level. SAHA (also called Vorinostat) is an FDA-approved drug for treatment of a cancer, and we are planning trials in NPC1 patients along with Drs. Forbes Porter and Marc Patterson.

The fellowship proposal is to study the mechanism by which histone deacetylase inhibitors are reducing cholesterol levels in patient fibroblast cells. We proposed that the mechanism by which SAHA is correcting cholesterol levels is by enhancing the expression of protein chaperones in the cells, which results in an increase in NPC1 protein. It turns out that many NPC1 mutations have some function if they can be delivered to the correct organelles in cells.

We are have tested more selective histone deacetylase inhibitors (with varying concentrations) for cholesterol reduction by an automated microscopy screening process. We have found more selective histone deacetylase inhibitors that work as well as SAHA. These more selective inhibitors might lead to a treatment of NPC1 disease with reduced side-effects.

We had previously checked for expression level of different chaperones in SAHA-treated cells and found an increase in BiP, a chaperone that may assist in getting NPC1 protein to the correct cellular organelles. We are testing if BiP is involved in reduction of cholesterol by overexpressing BiP in NPC1 cells. We found activation of another protein, IRE1α, after SAHA treatment, and we are investigating the role of this protein is involved in reducing cholesterol.